ORIGINAL ARTICLE

Infectious complications and antibiotic use in renal transplant recipients during a 1-year follow-up

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Objective To evaluate infectious complications and antibiotic use in 192 renal transplant recipients.

Methods Infectious complications and antibiotic use were monitored in all patients receiving renal transplantation at our center from 1992 to 1997. Risk factors for infectious complications were evaluated. Transplants and patient survival were monitored. The follow-up period was 1 year.

Results One-hundred and ninety-two patients received renal transplants during the study period. The mean duration of urethral catheterisation after transplantation was 10.5 days (SD = 5). Seventy-one per cent ($n = 137$) of patients had at least one infectious episode. In all, 284 infectious episodes were monitored. The most frequent infections were: urinary tract infections 61%, respiratory tract infections 8%, intra-abdominal infections 7%, and cytomegalovirus infection 8%. *Escherichia coli* and *Enterococcus faecalis* were the most frequently isolated microorganisms. Seventy-four per cent ($n = 142$) of patients received 314 antimicrobial courses (284 for therapy, and 30 for prophylaxis). Female gender and duration of urethral catheterisation were risk factors for urinary tract infection. Cytomegalovirus reactivation was associated with acute graft rejection and additional immunosuppressive therapy. Overall mortality was 4%. Infection-related mortality was 2.6%. Mortality was associated with Enterobacteriaceae in three patients, with *Pseudomonas aeroginosa* in one patient and with *Enterococcus faecalis* in one patient.

Conclusions The incidence of infectious complications remains high in renal transplant recipients. Most cases of mortality were associated with infections. Early removal of the urethral catheter to reduce the risk of urinary tract infections is recommended.

Keywords Renal transplantation, infectious complications, antibiotic use

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INTRODUCTION

Recipients of renal transplants are prone to develop infections because of the surgical procedure, immunosuppression, exposure to nosocomial pathogens, and the necessity for devices such as urinary catheters and intravascular lines in the first days post-transplantation [1]. Despite improvements of immunosuppressive therapy and surgical techniques, infections remain an important complication and have been associated with increased morbidity and graft rejection [2]. Urinary tract infections (UTIs) following transplantation are associated with tissue invasion by pathogens. This process might be strengthen by allograft rejection. The need for urethral catheterisation during the first days after transplantation, to protect the surgical anastomosis, represents an important risk for UTI [3–7]. However, the optimum duration for urethral catheterisation is unknown [8].

In addition to infection-related morbidity, infections may initiate allograft rejection, and have been associated with reactivation of latent cytomegalovirus (CMV) infection [9–11].

For all these reasons, prevention of infection in the early period after transplantation is important. Early removal of urethral catheters and the use of antibiotic prophylaxis have been advocated to reduce infectious complications [3–5]. In our center, renal transplant recipients receive a short regimen of antibiotic prophylaxis, and the urethral catheter is usually removed after 1 week. To assess the impact of the current policy in our center, we evaluated infectious complications and antibiotic use during 1-year follow-up after renal transplantation in 192 patients.

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PATIENTS AND METHODS

Study population

All patients receiving renal transplantation at the University Hospital Maastricht, The Netherlands, between January 1992 and January 1997, were studied prospectively for a 1-year period. During this period, all infectious episodes (both nosocomial and community-acquired infections), antibiotic use, transplant function, transplant survival and patient survival were monitored. The CMV serologic status of patients and donors was determined by measuring IgG antibodies to CMV using an ELISA method.

Immunosuppression and surgical procedure

One-hundred and fifty-six patients received prednisone (10 mg/day, and 5 mg/day after 6 months), azathioprine (1.5 mg/kg/day, oral) and cyclosporine (initially dosed to a serum level of 0.1–0.15 mg/L, and to 0.05–0.1 mg/L after 6 months) for immunosuppression. Thirty-six patients received azathioprine, prednisone, and tacrolimus (FK 506) (0.3 mg/kg/day, oral). Acute rejection was initially treated with three doses of 1 g of methylprednisolone on alternating days, and steroid-resistant episodes were treated with rabbit antithymocyte globulin (ATG) (initially 3 mg/kg/day, and then dosed on lymphocyte counts for 10 days).

The kidney graft was placed retroperitoneally in the right or left iliac fossa. The ureter was anastomosed to the recipient's bladder. The recipient's diseased kidney was not removed.

Perioperative antibiotic prophylaxis and postoperative care

All patients received a 1-day course of intravenous cefuroxime for antibiotic prophylaxis. The first dose (750 mg) was administrated preoperatively, and the second and third doses were administered 8 and 16 h postoperatively. Patients did not receive prophylactic agents for CMV and *Pneumocystis carinii*. Urine cultures were obtained twice a week during the hospital stay and whenever infection was presumed. The urinary catheter was usually removed after 1 week. After discharge from hospital, patients were regularly seen at the outpatient clinic, and, when indicated, cultures and other diagnostic measures were performed. No routine investigations were done for CMV and tuberculosis infection.

Definitions

The term infectious episode was used to indicate every episode of presumed or proved infection in which antibiotic therapy was initiated [12]. Six groups of infectious diseases were distinguished: UTIs, respiratory tract infections (RTIs), intra-abdominal infections, CMV infections, wound infections, and a group of miscellaneous infections.

Although the presence of bacteriuria would fulfill the criteria for UTI in renal transplant recipients [13], other criteria, such as pyuria (>10 leukocytes/mm^3) and fever, are frequently used for diagnosing UTI. In the present study, the CDC criteria, e.g. the clinical judgment of the physician in initiating therapy, was used as a definition for infection [12]. UTI was considered to be catheter related if the infection occurred during urethral catheterisation or within 24 h after catheter removal. RTIs were diagnosed according to the CDC criteria [12]. Intra-abdominal infectious episodes included local or generalised peritonitis, abdominal abscess formation, cholangitis, and pancreatitis. Wound infection was defined as the presence of purulent discharge from a surgical wound. CMV reactivation was defined by antigen detection or isolation of virus from any tissue or body fluid. The diagnosis of CMV disease was based on the presence of clinical symptoms (fever, malaise, arthralgias, myalgias and organ involvement) and detection of CMV in clinical samples (such as blood and bronchoalveolar lavage fluid).

Data analysis

Data were analyzed by the chi-square or Fisher exact test for dichotomous variables and the student's *t*-test for continuous variables. Odds ratio and 95% confidence intervals were calculated with SPSS-software (SPSS Inc., Chicago, IL, USA) as an estimate of the relative risk.

RESULTS

Patient population

The study population consisted of 192 renal transplant recipients (121 males and 71 females), with a mean age of 48 years (range, 17–73 years). Follow-up was complete for all patients for 1 year or until death if this occurred within the first year following transplantation. Twenty-eight patients (15%) received transplants from living donors, and the remaining 164 patients (85%) from non-living donors. Thirty-three patients (17%) received their second transplant, nine (5%) patients the third transplant, and two patients (0.5%) the fourth and the fifth transplant. The most frequent underlying causes of renal failure were chronic glomerulonephritis ($n = 47$), polycystic kidneys ($n = 28$), renal failure due to pyelonephritis ($n = 22$), nephrosclerosis ($n = 12$), IgA nephropathy ($n = 12$), diabetic nephropathy ($n = 9$), and other renal diseases ($n = 62$). The mean post-transplant hospitalisation time was 33 days (range 8–97).

Infectious complications

Seventy-one per cent ($n = 137$) of all patients had at least one infectious episode, with a mean of 1.5 episodes per recipient and 2.0 episodes per infected patient. In all, 284 infectious episodes

were monitored, and 146 (51%) occurred during hospital stay after transplantation.

Bacterial infections

Bacteria were considered the cause of infection in 249 (88%) of 284 episodes. Fifty-nine per cent ($n = 146$) of bacterial infectious episodes occurred during hospital stay after transplantation (Figure 1). Bacterial infectious episodes included: 173 episodes of UTI, 23 episodes of RTI, 21 intra-abdominal infections, six wound infections, and 26 unlabeled infection episodes. No infectious episodes with *Nocardia* and *Listeria* were monitored in the study population.

All wound infectious episodes and 71% (15/21) of intra-abdominal infectious episodes occurred during hospitalisation after transplantation. The incidence of wound infections was 3% ($n = 6$), and all episodes were superficial surgical wound infections that were treated with drainage and antibiotic therapy. Microbiological cultures of the surgical wounds revealed *Staphylococcus aureus* ($n = 3$) and Gram-negative rods ($n = 3$).

Nine intra-abdominal infectious episodes were surgery related. Nine intraperitoneal infections were associated with continuous ambulatory peritoneal dialysis. Three patients developed cholecystitis and had negative blood cultures.

During the 1-year follow-up, 103 recipients suffered 177 episodes of UTI (173 bacterial episodes and four fungal episodes). Fifty-six patients suffered one episode of UTI, and 47 patients had recurrent UTI. Overall incidences of UTI were 45% (87/192) during hospital stay after transplantation, and 54% (103/192) during 1-year follow-up. The incidence of UTI was higher in females than in males: 70% and 42%, respectively ($P < 0.0001$). The incidences of bacteriuria in diabetic patients and patients with polycystic kidneys were 67% (6/9) and 50% (14/28), respectively.

Escherichia coli and *Enterococcus faecalis* were the most frequently isolated microorganisms (Table 1). No methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci were isolated.

Fifty-two (47%) of 111 UTI episodes that occurred during hospital stay after transplantation were catheter related. The mean duration of urethral catheterisation was 10.5 days (SD = 5). Patients who suffered an episode of UTI postoperatively had longer duration of urethral catheterisation than those who did not develop UTI: 11.1 days (SD = 5) and 9.5 days (SD = 2.7), respectively ($P = 0.05$). Incidences of UTI were 2.6 episodes per 100 catheter-days and 1.4 episodes per 100 days without catheter, respectively ($P = 0.05$). Also, female gender was associated with occurrence of UTI during hospital stay after transplantation: 63% of females ($n = 45/71$) versus 35% of males ($n = 42/121$), $P < 0.001$. Other variables such as age, recurrent transplantation, cadaver kidney, diabetes mellitus and seropositivity to CMV were not associated with UTI. UTI was not associated with prolonged hospital stay ($P = 0.5$).

Most episodes of UTI were associated with bacteriuria ($n = 147$, 83%). Fifty-three episodes were asymptomatic bacteriuria. One hundred episodes were associated with pyuria (in 15 episodes, pyuria was the only present criterion). Only five episodes of UTI (3%) were associated with bacteremia. In 15 episodes, laboratory and microbiological criteria were absent, and UTI was presumed because of fever and by exclusion of other infections, such as RTI and intra-abdominal infection. In 85 (48%) episodes, both bacteriuria and pyuria were present (Figure 2).

Fungal infections

Eight episodes of fungal infection occurred (four episodes of UTI, three episodes of *Pneumocystis carinii* pneumonia, and one episode of oropharyngeal candidiasis). None of the patients had invasive fungal disease. *Candida albicans* was the causative pathogen in four cases, and *Candida* species in one episode. The five patients with candida infection were treated successfully with fluconazole 200 mg/day for 7 days. Three recipients developed *Pneumocystis carinii* pneumonia, all after hospital discharge, between day 60 and day 193 after transplantation. All three were treated successfully with co-trimoxazole 960 mg every 8 h for 2 weeks.

Viral infections

Eighty-five recipients were CMV seropositive, and 107 recipients were seronegative. Twenty-four patients (13%) developed a clinical episode of CMV infection (eight were recipient negative (R–) and donor negative (D–), 11 were R+D–, two were R+D+, and three were R–D+), occurring after a mean of 57 days after transplantation (range 23–199 days). Thirteen of the 24 CMV infectious episodes were considered to be reactivation. Eleven episodes were considered to be primary CMV infection. Patients with acute graft rejection had CMV reactivation more frequently than patients without allograft rejection: 20% (16/79) and 7% (8/113), respectively, odds ratio 2.9 (95% CI 1.3–6.4). In 16 of the 24 patients, CMV infection followed allograft rejection and increased immunosuppressive treatment (13 received methylprednisolone and three received methylprednisolone and ATG). One patient had severe infection (sepsis with *Escherichia coli*) before rejection occurred. All patients with CMV infection were treated with a 10-day course of ganciclovir.

Two patients developed herpes zoster infection (7–10 months post-transplantation), and one patient developed herpes simplex stomatitis (39 days post-transplantation). All three patients were treated with acyclovir for 10 days.

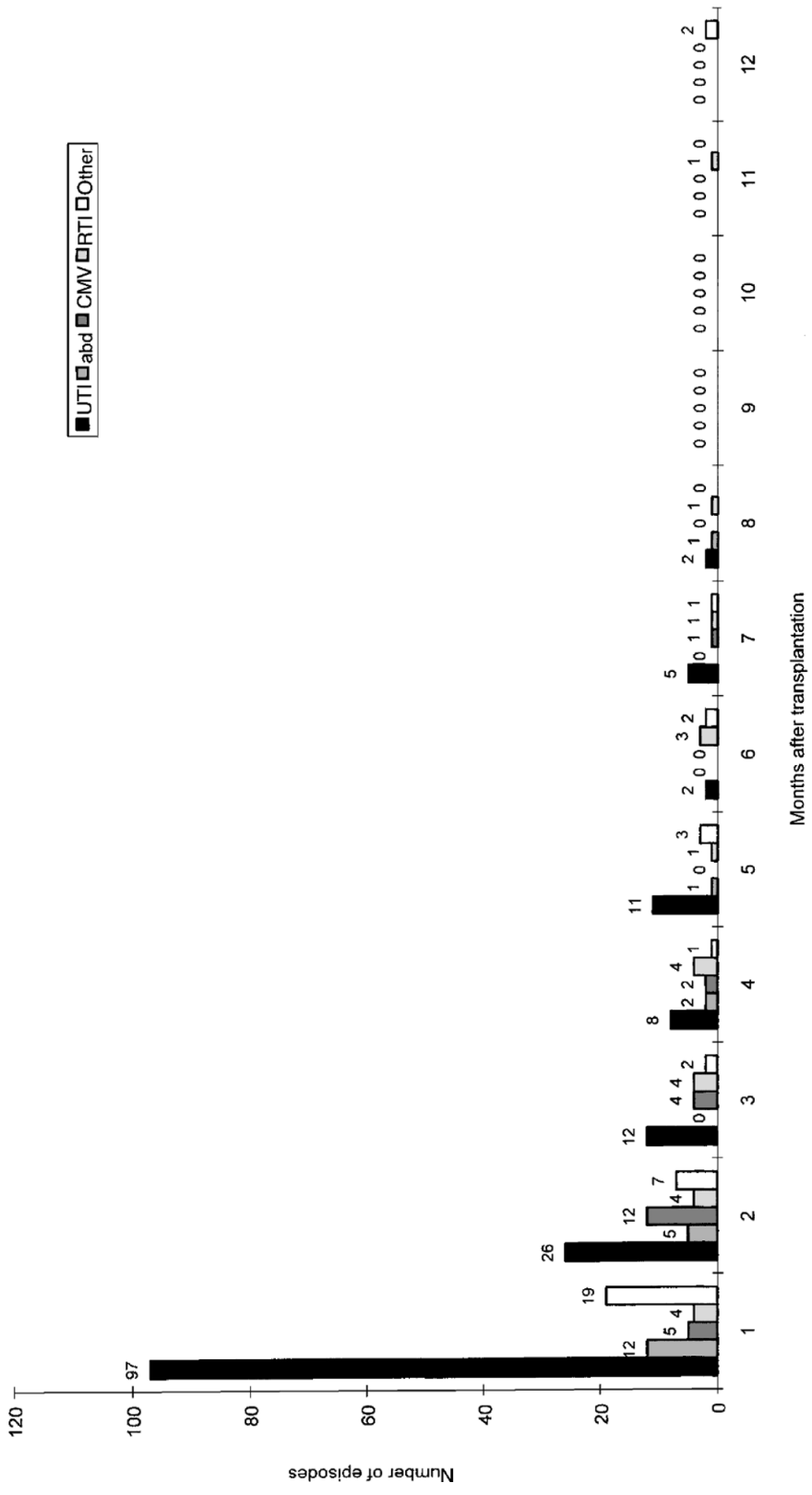

Figure 1 Timetable of infectious complications in the study population during 1-year follow-up. abd, intra-abdominal infections.

Table 1 Bacteria and fungi found in the study population

Microorganisms	Urinary tract infections		Intra-abdominal infections		Other infections	
	Urine culture	Blood culture	CAPD catheter	Abdominal pus	Other specimens[a]	Blood culture
Gram-negative bacteria						
Escherichia coli	65	2	2	2	4	1
Klebsiella pneumonia	14	–	1	2	1	–
Other Enterobacteriaceae	22	2	–	–	2	–
Pseudomonas aeruginosa	12	1	2	1	3	–
Haemophilus influenzae	–	–	–	–	2	–
Stenotrophomonas maltophilia	1	–	–	–	–	–
Gram-positive bacteria						
Staphylococcus aureus	1	–	4	4	2	1
Enterococcus faecalis	45	–	–	–	2	–
Staphylococcus epidermidis	6	–	–	–	2	1
Streptococci	–	–	–	–	1	1
Anaerobes	–	–	–	–	–	1
Yeasts						
Candida species	4	–	–	–	1	–
Pneumocystis carinii	–	–	–	–	3	–

[a]Other specimens include sputum, bronchoalveolar lavage fluid and intravascular devices.

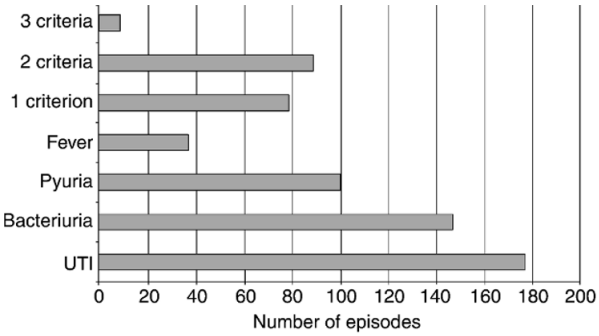

Figure 2 Bacteruria, pyuria and fever in episodes of urinary tract infection.

Use of antimicrobial agents

Overall, 142 (74%) of the 192 patients received 314 courses of antimicrobial treatment during follow-up; 284 for therapeutic purposes and 30 for prophylaxis.

In all, 137 patients received 284 courses of antimicrobial therapy for suspected or proved infections; 249 cases of bacterial infection, 27 cases of viral infection, and eight cases of fungal infection. In 271 (95%) of these courses, a single antimicrobial agent was prescribed, whereas two agents (β-lactam antibiotic and aminoglycoside) were prescribed in the remaining 13 (5%) courses.

Amoxicillin–clavulanic acid ($n=96$), ciprofloxacin ($n=47$), amoxicillin ($n=39$) and ganciclovir ($n=24$) were used most frequently. The mean duration of antimicrobial therapy was 14 days (range 1–99 days).

Antimicrobial agents were used in 33% of the postoperative hospitalisation-days and in 3.8% of all patient-days during 1-year follow-up. Fifty-six per cent of the courses were prescribed during hospital stay after transplantation.

Twenty-six patients received 30 courses of antibiotics for prophylaxis. In eight patients, isoniazid was prescribed because of a positive tuberculin test or history of tuberculosis. In 20 patients, a single dose of co-trimoxazole was given before removal of the urethral catheter, because the patients had UTI some days before catheter removal. Two patients received prophylaxis (ciprofloxacin) for several weeks because of recurrent episodes of UTI.

Rejection, graft failure and patient survival

Acute rejection occurred in 79 (41%) patients. All were treated initially with methylprednisolone, and 17 of them needed additional treatment with ATG. Anti-CMV prophylaxis was not given to patients with corticosteroid-resistant rejection. An association was found between rejection and CMV infection. Additional immunosuppression (16 patients) due to rejection predisposes to CMV reactivation, odds ratio 2.9 (95% CI 1.3–6.4). UTI was not associated with allograft rejection ($P=0.9$) or allograft survival ($P=0.3$).

Transplantation failed within hours in eight patients because of graft thrombosis. Twenty-nine (15%) renal grafts failed during 1-year follow-up. Overall mortality was 4% ($n=8$). These eight patients had experienced at least one infectious episode. Infection-related mortality was 2.6% ($n=5$). Of these

five patients, three developed sepsis and multi-organ failure, one had peritonitis, and one had intra-abdominal abscess. Mortality was associated with Enterobacteriaceae in three patients, with *Pseudomonas aeroginosa* in one patient, and with *Enterococcus faecalis* in one patient. Death occurred 55–95 days after transplantation (mean 80 days).

DISCUSSION

This study shows a high incidence of infectious complications in renal transplant recipients during a 1-year follow-up after transplantation. The occurrence of UTI was associated with the duration of urethral catheterisation and female gender. CMV reactivation was associated with acute allograft rejection.

A shorter duration of catheterisation could be an important measure to reduce UTI and antibiotic use in renal transplant recipients. A urethral catheter is needed after transplantation for maintaining urine drainage, and to prevent early obstruction, urinary leaks and vesical fistulas [7]. It has been demonstrated that the duration of urethral catheterisation is the most important risk factor for UTI, and advantages of early removal of the catheter have been emphasised [3–5,14]. Catheter removal after 8.2 days (SD 3.8) was associated with an incidence of UTI of 74% [4], whereas catheter removal within 36 h was associated with an incidence of 8% [3]. Ramsey et al. have shown that catheter removal within 48 h after transplantation reduces the UTI rate from 17% to 5.6% [14]. The duration of urethral catheterisation varies considerably in renal transplantation centers in Europe, but the duration is less than 1 week in 84% of these centers [8]. In our center, the duration of urethral catheterisation was long and was associated with the occurrence of UTI. Prolonged catheterisation is not indicated. The urethral catheter can be removed within the first week following transplantation [3–5].

Infection-related mediation of cytokines may trigger CMV replication [9,15]. However, in the present study, no association was found between severe infection and CMV reactivation. Only one patient developed CMV infection following severe infection. CMV reactivation was associated with acute allograft rejection and additional immunosuppressive therapy. A link between infection and allograft rejection has been suggested [16]. Immunosuppression, acute rejection and urosepsis may cause cytokine-mediated CMV reactivation. Conversely, CMV infection may induce cytokine release and subsequently cause allograft injury [16]. Whether asymptomatic CMV replication contributes to allograft injury remains unclear [16].

The importance of controlling antibiotic use and preventing the emergence of resistant microorganisms has been emphasised [16]. Our results show that antibiotic therapy was frequently initiated if bacteriuria was present, and severe infections were infrequently found. This suggests a low threshold for physicians to start antibiotic treatment. UTI seems not to increase hospital stay and graft failure. Therefore, we doubt the need to treat asymptomatic bacteriuria. A shorter duration of urethral catheterisation postoperatively may reduce the incidence of bacteriuria and subsequently the use of antibiotics.

High rates of wound infection after renal transplantation, despite perioperative antimicrobial prophylaxis, were reported in studies performed in the 1970s and 1980s [17,18]. The incidence of wound infection was low in the present study, as in other recent studies [19,20]. However, even without systemic perioperative prophylaxis, but only local antibiotic irrigation, the reported incidence of wound infection was only 2% in one study [21], suggesting that the lower incidences of wound infection in recent years may be partly due to improvements in surgical transplant techniques [21].

Infectious complications, especially UTI, remain a major cause of morbidity in renal transplant recipients, and lead to extensive use of antibiotics. Early removal of urethral catheters and efforts to optimise antimicrobial use are recommended.

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